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A spot diagnosis amidst red herrings

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Case

A white woman in her 70s with advanced Alzheimer's disease was referred to the hematology clinic for evaluation of a high hemoglobin (169g/L, NR 120-160) and red blood cell count (5.67 x10^{12}/L, NR 3.8-4.8) associated with a generalised itch, worse after a bath. On examination, she had a florid, erythematous macular eruption over the trunk and limbs (Figure, A), but no hepatosplenomegaly or lymphadenopathy. In addition to the high hemoglobin, a mild lymphocytosis (6.2 x 10^{9}/l, range 1.5-4.0) was noted with the lymphocyte morphology suggesting reactive changes. Skin biopsy (Figure, B) showed a normal epidermis with a pericapillary infiltrate of small lymphocytes restricted to the dermis and no leucocytoclastic vasculitis, fungal organisms or dermal mucin. The absence of cellular atypia and epidermal involvement suggested a diagnosis of lupus, or gyrate or annular erythema, and the need for clinicopathological correlation.

She was commenced on a topical emmolient, steroid creams and oral antihistamines; due to a sub-optimal clinical response, skin biopsy was repeated two months after the original procedure, but the histological appearances were unchanged. The hemoglobin continued to remain high and the lymphocyte count had increased to 9.0 x 10^{9}/l. A representative lymphocyte is shown (Figure, C).

What is the likely diagnosis?

A. Prolymphocytic leukaemia

B. Advanced cutaneous T-cell lymphoma/Sézary syndrome

C. Polycythemia rubra vera

D. Cutaneous lupus erythematosus

Diagnosis

A. Prolymphocytic Leukaemia (PLL).

Discussion

The blood film showed an excess of medium-sized lymphocytes with a round to oval nucleus, basophilic cytoplasm and prominent nucleolus (Figure, C), appearances that typify prolymphocytes. Immunophenotyping identified the expression of CD4 on lymphocytes along with the pan T-cell antigens CD2, CD3, CD5 and CD7, but no CD8, B cell or natural killer cell makers, supporting a diagnosis of T-PLL.

T-PLL, a rare lymphoid malignancy of older people (median age 61 years) can be misdiagnosed as an alternative mature T-cell neoplasm or even a benign disorder, particularly in patients with an atypical presentation.[1] Common features of T-PLL include a high lymphocytosis, bone marrow failure and splenomegaly, or lymphadenopathy, but pseudopolycythemia, mild lymphocytosis, erythroderma and pruritis in our patient made advanced cutaneous T-cell lymphoma/Sézary syndrome (CTCL) a diagnostic

consideration.[1-3] However, the malignant cells in CTCL have a hyperconvulated, cerebriform nucleus, distinguishing these from prolymphocytes. Moreover, the absence of epidermotropism and cellular atypia in the skin biopsy are characteristic of T-PLL. The preservation of CD7 expression on circulating and dermal prolymphocytes further supported a diagnosis of T-PLL over CTCL or adult T-lymphocytic leukemia/lymphoma (ATLL),[2,3] an alternative possibility. The patient's racial origin, low expression-intensity of CD25 on neoplastic cells and absence of eosinophilia also argued against ATLL.

The important learning point here is that with no unique antigen expression profile (except in a quarter of cases that co-express CD4 and CD8), the morphological recognition of circulating prolymphocytes is key to diagnosing T-PLL.[1] Thus, a failure to integrate the skin biopsy appearances with blood cytomorphology could have easily become a diagnostic pitfall, particularly since cytogenetic analysis was normal and non-contributory to the diagnosis. *FISH* probes failed to detect inversion of chromosome 14 (q11.2q32.1), the most frequent chromosomal abnormality in T-PLL that associates with TCL1 overexpression.[1-3,4] Nevertheless, *TCRB* and *TCRG* gene rearrangements confirmed the T-cell population to be clonal. Additional learning points relate to the original reason for referral to hematology: our patient was suspected to have myeloproliferative polycythemia (PRV) due to a high hemoglobin and itch, but patients with PRV generally *do not* have a rash.[5] It is likely that fluid loss due to erythroderma caused 'pseudopolycythaemia' in our patient; indeed,*JAK2* analysis was negative for mutations frequent in PRV.[6,7]

Cutaneous lupus erythematosus was unlikely as sun-exposed parts of the body were spared and typical histological features: lymphoid involvement of the dermo-epidermal junction, epithelial layer degeneration or dermal mucin deposits were absent,[8] as were serum autoantibodies commonly associated with connective tissue disorders.

Most patients with T-PLL require anti-leukemic therapy at presentation. Conventional chemotherapy and steroids have limited efficacy, but the anti-CD52 monoclonal antibody alemtuzumab can achieve responses rates of 70-90% when administered intravenously.[1,2] The disease response to alemtuzumab is of prognostic significance and supersedes the use of pre-treatment variables including total white count, lymphocyte-doubling-time and TCL1 expression-intensity, as an important determinant of survival.[1] However, responses are frequently not durable, and to optimise outcomes, consolidative treatment with autologous or allogeneic stem cell transplantation requires consideration in eligible patients.[1,2] Recent reports have indicated the effectiveness of the Bcl2 antagonist venetoclax[9] and JAK3 inhibitors[10] (following identification of JAK/STAT pathway mutations) in T-PLL, but the optimal positioning of newer drugs in treatment-algorithms requires investigation.[2]

Our patient's advanced cognitive impairment precluded a trial of therapy with alemtuzumab and her management focused exclusively on symptom-palliation. Eight months after the initial clinic visit, she presented with right sided periorbital swelling due to an abnormal soft tissue in the temporal and

zygomatic region compressing the eye-ball, and worsening lymphocytosis (13 x 10^9/l). Disease progression was rapid and she passed away in a hospice.

Declarations

The authors have no conflicts of interests to declare.

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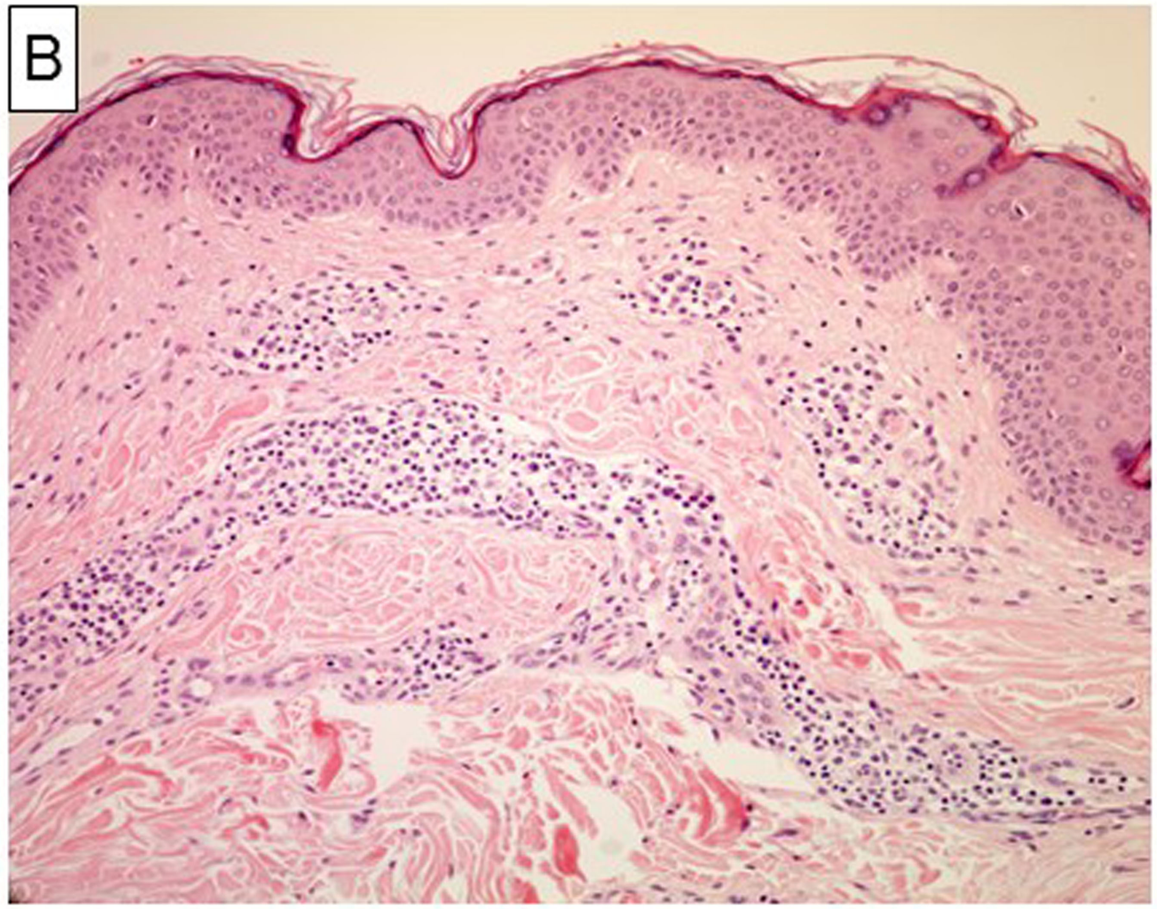
Figure. A. Skin image showing erythroderma. B. Section of skin biopsy showing a pericapillary infiltrate of small lymphoid cells restricted to the dermis (haematoxylin & eosin stain, original magnification x 200). C. Blood film image showing a typical lymphocyte (May Grünwald Giemsa stain, original magnification x 400).

A

B



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